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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,713	02/25/2002	Alan Colman	10758.105012 CON REV1002	9155

20786 7590 09/18/2008

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
09/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/080,713	COLMAN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133.

DETAILED ACTION

Applicants' Amendment and Response, filed 6/13/08, have been entered. Claims 62, 70, 90, 102, 131 and 133 are amended; claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are pending and under current examination.

New Matter

The prior rejection of claims 70-73 and 102-105 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claims which now recite placing a transgene adjacent to an endogenous promoter in the nuclear genome.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

Methods for producing a non-human transgenic mammal, comprising:

(a) *in vitro* targeted modification of an endogenous gene in the nuclear genome of a fibroblast to produce a genetically modified fibroblast;

(b) transferring the genetically modified fibroblast, or the nucleus thereof, to an enucleated oocyte to produce a viable nuclear transfer unit;

(c) activating the viable nuclear transfer unit;

(d) culturing the viable nuclear transfer unit to produce an embryo;

(e) transferring the embryo to a final surrogate mother, which is a suitable host for the non-human mammal to be grown to term; and

(f) allowing embryo to develop to term, thereby producing a non-human transgenic mammal.

The specification does not reasonably provide enablement for the breadth of modifying the nuclear genome of any somatic cell, other than fibroblast.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants have now amended the claims to recite that the placement of a gene adjacent to an endogenous promoter, that the oocyte, two-cell embryo, or zygote are all enucleated, and that the surrogate mother is a suitable host for the animal to be grown to term. These amendments overcome points 2-4 of recited on page 4 of the prior Office action, mailed 12/13/07).

Applicants argue that the Examiner is mistaken in limiting the scope to fibroblasts, rather than a broader set of somatic cells, because the term "fibroblast" relates to a general morphology of cells, and that the art would not place a premium on characterizing the given lineage of a given cell, as it would not be critical or even important in the field. Particularly, Applicants argue that the previously cited art refers to the term "fibroblast" as a cell that has a general appearance of a fibroblast, even when that may not be accurate. The Examiner had previously asked Applicants to provide support for the assertion that the cells in the post-filing art

are not necessarily fibroblast in origin, and Applicants argue that there is a lack of characterization, rather than a definitive characterization of the cells, due to the fact that the art has not generally cared whether the cells are indeed fibroblast, or just fibroblast-like in their growth characteristics. See pages 10-11 of the Response.

Response to Arguments. These arguments are not persuasive. There is no guidance to show that the art of record discusses using cells other than fibroblast, or fibroblast-like in methods of targeting cells. The art recites using fibroblast, or fibroblast-like cells. Clearly, the term "fibroblast" is an art-recognized term, and even if defined by morphology, one of skill in the art would readily recognize what a fibroblast was. Applicants have provide no further definition for the term "fibroblast" to show that the fibroblasts that Applicants have used in their examples are indeed fibroblasts. That is, using the same arguments as provided by Applicants, it would appear that same unpredictable factors brought up in the arguments – namely, that which one of skill would characterize fibroblasts based upon cell morphology, versus by cell lineage - could be similarly argued in view of Applicants' working examples using "fibroblast" cells. That is, given that Applicants' provide no more guidance for characterizing their fibroblast cells than that of the art and Applicants have provided no more guidance than that which is found in the art with regard to the cells that have been used in Applicants' working examples. The arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting cells taught in the art of record that are used are not fibroblasts.

Applicants' argue that Wilmut *et al.* discusses using cells that are "fibroblast-like" and appear to argue that the Wilmut's cells would not be considered fibroblast cells. See p. 12 of the Remarks. These arguments are not persuasive. Although Wilmut does not characterize their cells other than "fibroblast-like", clearly those of

skill in the art would recognize a fibroblast. The art recognizes various characteristics of fibroblasts, other than morphology, for example, Encyclopædia Britannica online (**fibroblast**. (2008). In *Encyclopædia Britannica*. Retrieved September 10, 2008, from Encyclopædia Britannica Online: http://www.search.eb.com/eb/article-9034174) teach that fibroblasts are:

> The principal nonmotile cells of connective tissue; **fibroblasts** are large, flat, elongated (spindle-shaped) cells possessing processes extending out from the ends of the cell body. The cell nucleus is flat and oval. Fibroblasts produce tropocollagen, which is the forerunner of collagen, and ground substance, an amorphous, gel-like matrix that fills the spaces between cells and fibres in connective tissue.

Clearly, fibroblasts have art-recognized qualities, other than morphology, such as the fact that they produce tropocollagen. Additionally the art recognizes various other characteristics; for example, Cancerweb (**fibroblast** (2008). Retrieved September 10, 2008 from Cancerweb online: http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=fibroblast) teach that fibroblasts secrete fibrillar procollagen, fibronectin and collagenase.

Applicants have argued that Kalluri and Neilson (2003) discuss the "epithelial to mesenchymal transition" (EMT) and Chang (2002) (see page11 of the Response). A copy of these references was not provided with Applicants' remarks or in any IDS, therefore these references and the arguments regarding this reference are not considered.

Applicants argue that the methods of preparing donor cells for NT involve taking a tissue (or entire fetus), cutting the tissue into small pieces and dispersing the cells, and the cells are then grown *in vitro*, and that cells after adherence are referred to as "fibroblasts". Applicants refer to Onishi *et al.*, Lai *et al.* and Dai *et al.* as support for the argument that the term fibroblast refers to morphological characteristics, and no analysis of cell type or identification (pp. 11-12). A copy of these references was not provided with Applicants' remarks or in any IDS, therefore these references and the arguments regarding this reference are not considered.

Applicants argue that the present Application describes methods of targeting two different kinds of somatic cells, including Example 5, which is directed to POME (primary ovine mammary epithelial) cells. Applicants have argued that the art prepares cells for NT by taking a tissue and cutting the tissue into small pieces and dispersing the cells, which are then grown *in vitro* and after adherence are referred to as fibroblasts. Applicants have argued that this technique does not provide any further investigation as to the cellular identity of the cells (p. 11, last ¶ of the Remarks). Example 5 of the specification appears to teach a similar method as described by Applicants (to produce fibroblasts), with regard to the production of POME cells. It appears that various pieces of mammary tissue was minced, and centrifugation was performed, the cells were then cultured (¶352), but no specific characterization of the cells was shown such that these cells were identified as mammary epithelial cells. Additionally, epithelial-mesenchymal transition (EMT) is a process wherein epithelial cells can give rise to fibroblasts. For example, Wikipedia (Epithelial-mesenchymal transition, retrieved September 10, 2008 from Wikipedia online: http://en.wikipedia.org/wiki/Epithelial-mesenchymal_transition) teaches that EMT is a characteristic of cells undergoing proliferation, by expanding the cells *in vitro*. There is no guidance in the specification to show that the POME cells are epithelial cells, and not cells that have gone through EMT. There is no guidance with regard to the characterization of Applicants' cells used in Example 5, with regard to particular morphology or markers to distinguish the cells as epithelial as opposed to fibroblasts.

Applicants have now amended the claims to recite modifying an "other somatic cell that has sufficient lifespan" to be useful for genetic modification. However, the specification does not provide any guidance to enable this amendment; particularly, the specification does not provide any guidance as to how to identify cells that have a sufficient lifespan, and provided a specific definition for the phrase "sufficient lifespan". For example, does the cell need to divide

sufficiently to provide a cell line, or does it need to be kept alive for a long time? Cells such as neurons do not divide, but certainly could have a long lifespan. The specification provides no guidance as to how to enable identification of a somatic cell that has a sufficient lifespan to be useful for genetic modification; therefore, this embodiment is not found to be enabled.

Accordingly, for the reasons cited above, it would have required undue experimentation for the skilled artisan to carry out the claimed methods, with a predictable degree of success, to implement the invention as claimed.

Claim Rejections - 35 USC § 112

The prior rejection of claims 62, 70 and 102, under 112, 2nd paragraph is withdrawn in view of Applicants' amendment to the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is new ground of rejection necessitated by Applicants' Amendment to the claims.

Claim 62 is unclear. Step (d) has been amended to recite that the suggoate mother is a suitable host for the animal to be grown to term. However, the preamble, and final steps of the claim are directed to producing a non-human mammal. Therefore, the method step of (d) in claim 62 does not fully relate to other method steps, because it is broader and encompasses animals which are not mammals, which would then be used to develop into a non-humanmammal. Appropriate correction is required. Claims 63, 65, 66, 70-73, 75-79, 82, 87-89, 121-

125 depend from claim 62. Independent claims 90 and 133 have the same amended claim language as claim 62, and therefore, are likewise unclear. Claims 99, 100, 102-110, 113, 118-125 depend from claim 90.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the

alternative, under 35 U.S.C. 103(a) as obvious over Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS).

Applicants' Arguments. Applicants argue that Campbell does not have any additional results that would support targeted transgenic animals from somatic cells, and they do not dispel the substantial uncertainty that one in the art would have had as to whether any techniques could be used to make targeted transgenic animals using somatic cell nuclear transfer, let alone any specific methods that would have enabled anyone to actually produce such animals with even a minimal expectation of success. See p. 13 of the Response.

Applicants argue that there was a strong belief in the art that somatic cells grown in culture for significant periods were no longer useful in producing transgenic animals. Applicants argue that this shows that Campbell is non-enabling because there is substantial uncertainty as to the success of the process. Applicants argue that it was well-known that the ability to target versus randomly integrate into somatic cells was much lower than in embryonic stem cells, and that primary cells have a lower frequency of homologous recombination than immortalized cells (pp. 13-14). Applicants argue that Campbell does not provide any techniques to overcome the art-recognized difficulties, and that there are no statements in Campbell that would have been considered in the art to overcome the problems of low targeting frequency and early senescence that were well-known in the art. Applicants argue that the passages in Campbell that relate to genetic modification refer to the fact that successful NT is a step towards successful generation, and that Applicants argue that Campbell only teach a mere desirability, but is not sufficient to enable a targeted modification of a somatic cell and its subsequent use in NT. See p. 15 of the Response.

Similarly, Applicants argue that Campbell fails as a reference under 103(a) for much the same reasons as it fails under §102, namely because the reference simply provides no more than a hoped for result in a field in which the hoped for

result was considered to be outside of the ability of the ordinarily skilled artisan. Applicants argue that the Campbell does not overcome the art-recognized difficulties in prolonged cell culture (pp. 15-16 of the Response). Applicants argue that the desirability of targeted genetically modified large animals was well documented in the prior art however, even after Campbell's filing, it took over four years to develop the presently claimed techniques to provide viable, genetically targeted animals using SCNT. See p. 16 of the Response. Applicants argue that the present invention fulfills the long-felt need to develop targeted genetically modified large animals and supports the non-obviousness of the present invention over Campbell. See pp. 16-17 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. Campbell fulfill the limitations of the claims. There is nothing that distinguishes the claimed invention from that which is taught by Campbell. Particularly, Campbell teach that transgenic animals can be made, by using a cell such as a fibroblast. This is exactly what is claimed. Applicants have not distinguished their invention from that which is taught and suggested by Campbell. Although one of skill in the art would recognize the general problems of the art, with regard to gene targeting somatic cells, Campbell provides specific guidance as to the cell types to use, as well as the techniques to produce the desired result. Campbell provides the requisite teachings to fulfill the claim limitations because they teach or suggest each method step required by the claims. See *Integra Life Sciences I Ltd. v. Merck KGaA,* 50 USPQ2d 1846 (DC SCalif, 1999) which teaches that a reference teaching a process may anticipate claims drawn to a method comprising the same process steps, despite the recitation of a different intended use in the preamble or the later discovery of a particular property of one of the starting materials or end products. See also *Ex parte Novitski,* 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993), which teaches that a reference teaching a claimed process, wherein one of the claimed properties of a product used in the prior art process is

inherent but undisclosed by the reference, may be properly applied as art against the claimed process.

Although Applicants argue that Campbell does not provide any techniques to overcome the art-recognized difficulties in gene targeting somatic cells, and provide art to support these arguments (see p. 14 of the Response), it is noted that the claims do not provide any steps that are distinguished from the teachings of Campbell. Therefore, the suggestion that Campbell is unpredictable, or non-enabling, suggests that Applicants' invention might similarly be unpredictable or non-enabling. The method steps, as instantly claimed, are not distinguished from the teachings of Campbell, and therefore, the prior rejection of record is maintained. If Applicant feels the art is not enabling, and the claims cannot be distinguished from the art, then Applicant's claims must also lack enablement. It is up to Applicant to amend the claims to be enabled and distinguish from the art. However, the effect is inherent in the art applied, as the case law states if an invention and the art have the same structure all properties of one will be found in the other. Applicant is encouraged to amend the claims to overcome the art.

Applicants have pointed to Arbones(1994), Finn (1989), Thyagarajan (1996) and Suraokar and Bradley (2000), Porter (1997), but a copy of these references was not provided with Applicants' remarks or in any IDS, therefore these references and the arguments regarding this reference are not considered. Applicants have pointed to the Surani Declaration, however, this Declaration was not provided with Applicants' response, therefore the Declaration has not been considered. See pages 14-15 of the Response.

Accordingly, this rejection is maintained.

Claims 76-79, 107-110, 123-124 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell as applied to claims 62, 63, 65, 66, 75, 76, 82, 87-

90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 above, and further in view of d'Apice *et al.* (**U.S. Pat. No. 5,849,991** published December 15, 1998).

Response to Arguments. Applicants have provided the same arguments with regard to Campbell, which have been addressed above. Applicants argue that d'Apice discuss providing homozygous mice that lack a particular gene, alpha 1-3, galactosyltransferase, using ES cells. Applicants argue that for large animals, for which ES cells were not available, there is no additional teaching in d'Apice that would suggest that a technique had been developed to overcome the hurdle of somatic cell senescence. See p. 17 of the Response. It is noted, that d'Apice is not relied upon with regard to producing animals by NT. Campbell provides the required teachings for producing transgenic mammals via NT, and d'Apice discusses producing mammals, including but not only, mice, lacking alpha 1-3 galactosyltransferase (col. 4, lines 54-60). Additionally, it is noted that the claims are not limited to "large animals" but are directed to any non-human transgenic mammal. Therefore, the combination of the references sufficiently motivate the skilled artisan to arrive at the claimed invention, given Campbell's teachings for increasing efficiency of producing transgenic animals, and further, given d'Apice's teachings for the need in the art to produce animals whose organs can then be used for xenotransplantation, wherein the knockout of the alpha 1-3 galactosyltransferase gene reduces or eliminates the hyperacute rejection response.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 70, 73, 77, 102, 105, 107, 108, 125 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell as applied to claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 above, and further in view of Kucherlapati *et al.* (**WO 94/02602**, published February 3, 1994).

Response to Arguments. Applicants have provided the same arguments with regard to Campbell, which have been addressed above. Applicants argue that Kucherlapati teach techniques which could be used in animals in which ES cells could be used to make transgenic animals. Applicants argue that the techniques of Kucherlapati are not applicable to the instant invention, and that the major obstacle in production of cloned large animals has traditionally been that the ES cells are not generally available. These arguments are not persuasive. Campbell is used to provide guidance to producing cloned, transgenic animals. The Examiner notes that the claims are not solely limited to large animals. Therefore, the combination of references sufficient motivate the skilled artisan to arrive at the claimed invention. Accordingly, given the combined teachings of Campbell and Kuncherlapati, it would have been obvious for one of ordinary skill in the art to use the technology of Campbell, and inactivate an endogenous Ig gene in a somatic cell, with a reasonable expectation of success. Although Kuncherlapati teach knockout of the endogenous Ig in mouse ES cells, Campbell provides the teachings and suggestion to use a somatic cell, and then use the modified somatic cell in methods of NT to produce transgenic animals. One of ordinary skill in the art would have been sufficiently motivated to knockout an endogenous Ig gene, as supported by Kuncherlapati, who teach that it is an art-recognized goal to produce xenogeneic specific binding proteins, such as human monoclonal antibodies (p. 2, lines 23-32) by production of transgenic animals. Additionally, one of skill in the art would have been motivated to modify the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by Kuncherlapati, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize utilizing various marker genes in order to select for clones when performing transfection experiments.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 70, 72, 102, 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell as applied to claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 above, in further view of US Pat. No. 6,013,857 (Filed June 5, 1995, Issued January 11, 2000). This is a new ground of rejection necessitated by Applicants' amendments to the claims.

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome, wherein the promoter is a milk promoter. However, prior to the time of the claimed invention, the '857 patent discusses producing transgenic bovines for producing recombinant polypeptides in milk (Abstract). Particularly, they teach using endogenous milk regulation (*i.e.*, promoter) sequences (col. 8-9, bridging ¶).

Accordingly, it would have been obvious for one of ordinary skill in the art, to modify the methods, as taught by Campbell, to place a transgene of interest adjacent to an endogenous promoter, such as a milk promoter, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification, in view of the '857 patent which teaches that these methods would be used in order to produce recombinant polypeptides of interest from transgenic bovine species and isolate the recombinant polypeptide from milk (Abstract).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 70, 71, 102 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell as applied to claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 above, in further view of Bedalov (Journal of Biol. Chem., 269(7): 4903-4909, 1994) when taken with Rossert (The J. of Cell Biol. 129(5): 1421-1432, 1995).

This is a new ground of rejection necessitated by Applicants' amendments to the claims.

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome wherein the promoter is a collagen gene promoter. However, prior to the time of the claimed invention, Bedalov discuss a transgene containing the COL1A1 promoter fused to a reporter gene and discuss its expression in a variety of mesenchymal cell types, including fibroblasts, osteoblasts and odontoblasts (see p. 4903, 1st col., 1st ¶). Bedalov teaches that transgenic mice which have ~3.5 kb of COL1A1 upstream promoter have strong expression of the reporter gene in high collagen producing tissues, such as tendon, bone and skin (p. 4903, col. 2, first full ¶). Bedalov teach that the COL1A1 construct, including the COL1A1 promoter confers tissue-specific expression in transgenic animals, with no aberrant expression (see pp. 4908-4909, bridging sentence). Bedalov suggest that making transgenic animals with genome-integrated transgenes would allow for further analysis of endogenous gene expression and would provide a model that is more biologically representative for the interaction of trans-acting factors with the sequences in the promoter (p. 4909, 1st full ¶, last sentence).

Accordingly, it would have been obvious for one of ordinary skill in the art, to utilize the teachings to make a transgenic, gene targeted animal, by nuclear transfer, as taught by Campbell, and specifically target a transgene under the expression of a collagen promoter, such as that taught by Bedalov, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of Bedalov's teachings, which show an art-recognized need to further analyze the expression of the COL1A1 promoter in transgenic animals, and additionally, in view of Rossert, who teach that the precise sequences responsible for the lineage-specific expression of the collagen promoter have not been defined (p. 1421, col. 2, last bridging ¶). Thus, the claimed

invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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